VOLUME 3 OF 5

Title

Health Effects Waiver Requests for Copper (II) Oxide in Corning® Antimicrobial Particles

Data Requirement

Health Effects Test Guidelines – OCSPP Series 870

Acute Oral Toxicity – OCSPP 870.1100
Acute Dermal Toxicity – OCSPP 870.1200
Acute Inhalation Toxicity– OCSPP 870.1300
Primary Eye Irritation – OCSPP 870.2400
Primary Dermal Irritation OCSPP 870.2500
Dermal Sensitization – OCSPP 870.2600
90-Day Oral Toxicity – OCSPP 870.3100
90-Day Dermal Toxicity – OCSPP 870.3250
90-Day Inhalation Toxicity – OCSPP 870.3465
Prenatal Developmental Toxicity Study – OCSPP 870.3700
Reproduction and Fertility Effects - OCSPP 870.3800
Carcinogenicity – OCSPP 870.4200
Bacterial Reverse Mutation Test – OCSPP 870.5100
In vitro Mammalian Cell Gene Mutation Test – OCSPP 870.3500
In vitro Mammalian Chromosome Aberration Test – OCSPP 870.5375
Acute Neurotoxicity – OCSPP 870.6200
Immunotoxicity – OCSPP 870.7800

Author

Leslie E. Patton, Ph.D.

Study Completed on

September 15, 2015

Study Sponsor

Corning Incorporated
1 Riverfront Plaza
Corning, NY 14831

Prepared by

Technology Sciences Group Inc.
1150 18th St. N.W. Suite 1000
Washington, D.C. 20036

Statement of No Data Confidentiality Claims

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA Section 10 (d)(1)(A), (B), or (C).

COMPANY/SUBMITTER: Corning Incorporated
1 Riverfront Plaza
Corning NY 14831

COMPANY REPRESENTATIVE: Megan E. Pletka Date: 9/23/2015
Megan E. Pletka

Good Laboratory Compliance Statement

This study does not meet the requirements of 40 CFR Part 160 and differs in the following ways:

1) No quality assurance unit was in place.
2) No study director was assigned.

SPONSOR /SUBMITTER: Megan E. Pletka Date: 9/23/2015

Megan E. Pletka

Introduction

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use in a material preservative End Use Product (EP) called Corning® Antimicrobial Particles. The proposed EP is made by combining cupric oxide (Cu(II)) with aluminoborosilicate glass and heating the mixture to very high temperatures (1400-1650°C), at which point the Cu(II) becomes embedded into the glass matrix. The molten mixture is then rapidly cooled and milled into a powder (Corning 2015). During this process, the cupric oxide has transformed into Cu^{2+} ions. In the resulting EP, the copper and glass cannot readily be separated by mechanical means. Overtime, copper ions will very slowly exchange with other ions at the surface of the glass, which accounts for the EP's antimicrobial properties.

The EP is intended for addition to paint or plastic. For paint, it will function as an in-can preservative against mold and mildew as well as functioning as a preservative for dry paint film on surfaces. Paints containing this EP will be applicable to household and industrial products such as ceramics, wood, plastic, cement plaster and other building materials. The paint is not intended for use on boats, docks, or other surfaces that result in fresh water or marine water exposure. The EP can also be incorporated into plastic during the manufacturing process to protect the finished goods made from this plastic against mold and mildew.

The present volume comprises rationales for data requirements that must be met for the TGAI copper (II) oxide. Some of the conditional testing requirements are not addressed in the rationales presented here because the notes in the relevant data tables indicated they were not necessary. The table below lists the data requirements that we felt did not require addressing and the note number from the CFR data table explaining why, along with a brief explanation for our not addressing the endpoint with a formal rationale.

Guideline No.	Data Requirement	Reference Note #	Reason conditional test is not required
40 CFR 158.2230 – Toxicology			
870.3150	90-Day oral toxicity - nonrodent	10	TGAI is not highly bioaccumulative or slowly eliminated.
870.6300	Developmental neurotoxicity	30	No neurological effects associated with copper pesticides (see EPA RED, 2006)
870.4100	Chronic oral toxicity—rodent	20	The use of this pesticide is not likely to result in repeated human exposure over a considerable portion of the human lifespan. The use of the pesticide does not require that a tolerance, tolerance exemption, or food additive regulation or clearance be established.
870.7485	Metabolism and pharmacokinetics	35, 39	The chronic toxicity and carcinogenicity studies are not required. Significant adverse effects are not seen in available toxicology studies (EPA 2006)
870.7600	Dermal penetration	37	See rationale for 90-day dermal study

Rationales for Antimicrobial Data Requirements – *Health Effects*

OCSPP Guideline: 870.1100
Data Requirement: Acute Oral Toxicity

Summary:

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use as an antimicrobial preservative for incorporation into paints or plastics which can then be applied or incorporated into other household and industrial products such as ceramics, wood, plastic, cement plaster and other building materials to protect against mold and mildew. Corning Inc. requests that the requirement for an Acute Oral Toxicity study (OCSPP 870.1100) for copper (II) oxide be satisfied by existing data and information based on the facts that: 1) copper is an endogenous biochemical; 2) copper compounds are exempt from the requirement of a tolerance for most uses; 3) there is a long history of safe commercial and industrial use of copper; and 4) the potential for exposure to copper is low for the proposed use.

Response to Data Requirement:

As an endogenous compound, copper is an integral part of many proteins and enzymes important to cellular respiration, cellular energy metabolism, connective tissue biosynthesis and iron metabolism (WHO 1998). An oral daily uptake of 0.9–3 mg/day is considered necessary to avoid copper deficiency (ATSDR 2004; IOM 2015). Copper (II) compounds are not significantly toxic as demonstrated by the fact that a variety of copper-containing compounds are exempt from the requirement of a tolerance, including metallic copper in the form of chelates of copper citrate and copper gluconate (40 CFR 180.1021 (a) (b) (c) (d); EPA, 2006).

An evaluation of copper in the Human Health Chapter of the EPA Reregistration Eligibility Decision (RED) document indicates that no toxicological endpoints were established for copper residues (EPA 2006). Cupric oxide was considered Toxicity Category IV for oral exposure. Similarly, in the European Chemicals Agency (ECHA) dossier for cupric oxide, an OECD guideline 423 (Acute Toxic Class Method) study is described in which an LD50 of >2500 mg/kg bw was established for cupric oxide (ECHA 2015).

Copper has long been used in ceramics for imparting colors into glasses, glazes and enamels (CDA 2015). It is also incorporated into mineral supplements for animal diets. Other copper compounds are registered for antimicrobial pesticidal use in wood paint, glue, building materials, construction materials, and water treatment wherein the active cupric ion functions as a mildewcide, bactericide, or anti-fouling agent (EPA 2006).

Oral exposure to copper (II) oxide is not anticipated for the end use associated with this TGAI. When copper oxide mixed with aluminoborosilicate glass is heated to very high temperatures, copper ionizes and becomes a part of the glass matrix; the copper and

glass cannot readily be separated. Therefore, the potential for oral exposure to copper is very low.

Conclusion

Corning Inc. requests that the requirement for an Acute Oral Toxicity Study for copper (II) oxide be satisfied based on the fact that copper is an endogenous compound that is a dietary requirement. It is considered toxicity category IV and there is a long history of safe use of copper in a range of products. Finally, the potential for oral exposure to copper is low from the proposed end use. An acute oral toxicity study is not necessary to demonstrate the safety of oral exposure to copper (II) oxide.

References

40 CFR 180.1021 Copper; exemption from the requirement of a tolerance.

Agency for Toxic Substances and Disease Registry (ATSDR). 2004. Toxicological profile for copper (update). Chapter 3: Health effects. US Department of Health and Human Services. Public Health Service.

Copper Development Association (CDA). 2015. Uses of Copper Compounds: Other Copper Compounds.

Institute of Medicine (IOM). 2015. Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Vitamins Food and Nutrition Board, Institute of Medicine, National Academies. Accessed July 2015.

U.S. EPA. 2006. Reregistration Eligibility Decision (RED) for Coppers.
EPA 738-R-06-020. July 2006.

World Health Organization (WHO).1998. Environmental Health Criteria 200. Copper. Section 6.1: Essentiality. IPCS, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland..

OCSPP Guideline: 870.1200
Data Requirement: Acute Dermal Toxicity

Summary:

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use as an antimicrobial preservative for incorporation into paints or plastics which can then be applied or incorporated into other household and industrial products such as ceramics, wood, plastic, cement plaster and other building materials to protect against mold and mildew. Corning Inc. requests that the requirement for an Acute Dermal Toxicity study (OCSPP 870.1200) for copper (II) oxide be satisfied by existing data and information based on the facts that: 1) copper is an endogenous biochemical; 2) the dermal toxicity of copper has been characterized; 3) there is a long history of safe medical, commercial and industrial use of copper; and 4) the potential for systemic exposure to ionic copper via dermal contact is low for the proposed use.

Response to Data Requirement

As an endogenous compound, copper is an integral part of many proteins and enzymes important to cellular respiration, cellular energy metabolism, connective tissue biosynthesis and iron metabolism (WHO 1998). Copper compounds are of low toxicity as demonstrated by the fact that a variety of copper-containing compounds are exempt from the requirement of a tolerance.

The evaluation of copper in the Human Health Chapter of the EPA Reregistration Eligibility Decision (RED) document indicates that no toxicological endpoints were established for copper residues (EPA 2006). The RED characterizes cupric oxide as Toxicity Category III for the dermal exposure route (EPA 2006). In the European Chemicals Agency (ECHA) dossier for cupric oxide, an OECD guideline 402 study is described in which a dermal LD50 of >2000 mg/kg bw was established for cupric oxide (ECHA 2015). In addition, copper is used in wound dressings and ointments, as a topical astringent/antiseptic, and in commercial skin care products (Borkow and Okon-Levy 2010; Fiume et al. 2014; Dresher 2006). Other copper compounds are registered for antimicrobial pesticidal use in wood paint, glue, building materials, construction materials, and water treatment wherein the active cupric ion functions as a mildewcide, bactericide, or anti-fouling agent (EPA 2006). There is no toxicological concern from potential dermal exposure to copper.

Systemic exposure to copper (II) oxide is unlikely for several reasons. In vitro studies and in vivo dermal application of copper salts or dermal exposure to metallic copper fumes suggest that copper is poorly absorbed through the skin (SCOEL 2014; ATSDR 2004). In one study, less than 6% of copper deposited on *ex vivo* human skin samples was absorbed (SCOEL 2014). Thus, systemic copper exposure is unlikely. In addition, there is very little potential for exposure to copper from the end use product. When copper oxide mixed with aluminoborosilicate glass is heated to very high temperatures, copper ionizes

and becomes a part of the glass matrix; the copper and glass cannot readily be separated. Therefore, the potential for dermal exposure to copper is very low for this use.

Conclusion

Corning Inc. requests that the requirement for an Acute Dermal Toxicity Study for copper (II) oxide be satisfied based on the fact that copper is an endogenous biochemical with a long history of safe use in a range of products in which dermal exposure occurs regularly. The dermal toxicity of copper has been characterized and the potential for systemic exposure to copper is low via the dermal route. An acute dermal toxicity study is not necessary to demonstrate the safety of dermal exposure to copper (II) oxide.

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2004. Toxicological profile for copper (update). Chapter 3: Health effects. US Department of Health and Human Services. Public Health Service.

Borkow and Okon-Levy 2010. Copper Oxide Impregnated Wound Dressing: Biocidal and Safety Studies. Wounds 22(12):301-310.

Drescher WH. 2006. Copper and Your Skin: Facelift In A Bottle. Copper Applications in Health and Environment Area. Copper Development Association Newsletter.

Fiume et al. 2014. Safety assessment of citric acid, inorganic citrate salts, and alkyl citrate esters as used in cosmetics. IJT 33(Suppl.2):16-46, 2014

Scientific Committee on Occupational Exposure Limits (SCOEL). 2014. Recommendation from the Scientific Committee on Occupational Exposure Limits for Copper and its inorganic compounds. European Commission. SCOEL/SUM/171. March 2014

U.S. EPA. 2006. Reregistration Eligibility Decision (RED) for Coppers. EPA 738-R-06-020. July 2006.

World Health Organization (WHO).1998. Environmental Health Criteria 200. Copper. Section 6.1: Essentiality. IPCS, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland..

OCSPP Guideline: 870.1300
Data Requirement: Acute Inhalation Toxicity

Summary:

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use as an antimicrobial preservative for incorporation into paints or plastics which can then be applied or incorporated into other household and industrial products such as ceramics, wood, plastic, cement plaster and other building materials to protect against mold and mildew. Corning Inc. requests that the requirement for an Acute Inhalation Toxicity study (OCSPP 870.1300) for copper (II) oxide be satisfied by existing data and information based on the facts that: 1) copper is a ubiquitous naturally occurring metal that is exempt from the requirement of a tolerance for most uses; 2) the acute inhalation toxicity of copper compounds has been established previously; and 3) there is no potential for inhalation exposure to copper for the present use.

Response to Data Requirement:

Copper is of low toxicity as demonstrated by the fact that a variety of copper-containing compounds are exempt from the requirement of a tolerance, including metallic copper in the form of chelates of copper citrate and copper gluconate (40 CFR 180.1021 (a) (b) (c) (d); EPA, 2006). The evaluation of copper in the Human Health Chapter of the EPA Reregistration Eligibility Decision (RED) document indicates that no toxicological endpoints were established for copper residues (EPA 2006). The RED characterizes cupric oxide as Toxicity Category III for the inhalation exposure route (EPA 2006). Thus there is low toxicological concern from potential exposure by inhalation.

Systemic exposure to copper (II) oxide through the inhalation route of exposure is not anticipated for consumers. During the manufacture of the EP, copper oxide is mixed with aluminoborosilicate glass and heated to very high temperatures. Copper ionizes and becomes a part of the glass matrix; the copper and glass cannot readily be separated. The copper glass is mixed into paint or plastic before consumers can interact with it. Therefore, the potential for inhalation exposure to copper is negligible for this use.

Conclusion:

Corning Inc. requests that the requirement for an Acute Inhalation Toxicity Study for copper (II) oxide be satisfied based on the fact that there is a long history of using copper in pesticides, copper inhalation toxicity has been classified and no toxicological endpoint was established. No significant exposure to copper is anticipated for the present use. Therefore, an acute inhalation toxicity study is not necessary for copper (II) oxide.

References:

U.S. EPA. 2006. Reregistration Eligibility Decision (RED) for Coppers. EPA 738-R-06-020. July 2006.

OCSPP Guideline: 870.2400
Data Requirement: Primary Eye Irritation

Summary:

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use as an antimicrobial preservative for incorporation into paints or plastics which can then be applied or incorporated into other household and industrial products such as ceramics, wood, plastic, cement plaster and other building materials to protect against mold and mildew. Corning Inc. requests that the requirement for a Primary Eye Irritation study (OCSPP 870.2400) for copper (II) oxide be satisfied by existing data and information based on the facts that on the facts that: 1) copper is a ubiquitous naturally occurring metal that is exempt from the requirement of a tolerance for most uses; and 2) the ocular irritation properties of copper (II) oxide have been established previously with animal testing.

Response to Data Requirement:

Copper is of low toxicity as demonstrated by the fact that a variety of copper-containing compounds are exempt from the requirement of a tolerance. The recent evaluation of copper in the Human Health Chapter of the EPA Reregistration Eligibility Decision (RED) document indicates that no toxicological endpoints were established for copper residues (EPA 2006). Thus there is no concern from potential ocular exposure to copper per se. The RED indicates copper (II) oxide is Toxicity Category III (EPA 2006) for this endpoint.

In the European Chemicals Agency (ECHA) dossier for cupric oxide, an OECD guideline 405 study was described (ECHA 2015). A powder of cupric oxide (~38 mg; purity 97.7%) was instilled into the eye of three male New Zealand white rabbits. Ocular damage was assessed after 1, 24, 48 and 72 hours and reversibility was determined after 7 days. Eyes were not rinsed at any time point. Effects in the first 72 hours included diffuse corneal opacity (one eye), iridial inflammation, and moderate conjunctival irritation. All treated eyes appeared normal at the 7-day observation time point. Copper oxide produced a maximum group mean score of 13.0 and was classified as a mild irritant (Class 4 on a 1 to 8 scale) to the rabbit eye according to a modified Kay and Calandra classification system. ECHA rated the study “1” on the Klimisch evaluation scale, indicating reliability without restriction (ECHA 2015).

Product formulation also effects ocular irritation. EPA (2006) states that “copper compounds formulated as dusts and as powders are irritating to the eyes.” Rather than systemic, these effects are a result of the body’s mechanisms to reduce excessive exposure to copper. Ocular exposure to dusts or powders may hurt the eyes as a result of mechanical irritation. This is not unique to copper (II) oxide.

Conclusion:

Corning Inc. requests that the requirement for a Primary Ocular Irritation Study for copper (II) oxide be satisfied based on its extensive history of use and the fact that the ocular irritation properties have been characterized previously. An additional primary ocular irritation study is not necessary for copper(II) oxide.

References:

European Chemical Agency (ECHA). 2015. Dossier for Copper(II) Oxide. Accessed July 13, 2015. Available: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9eb99a84-d8fb-732d-e044-00144f67d031/AGGR-cd152e28-9bb4-4a1f-8838-d3ff97576f34_DISS-9eb99a84-d8fb-732d-e044-00144f67d031.html#GEN_APPL_SUM_HD

U.S. EPA. 2006. Reregistration Eligibility Decision (RED) for Coppers. EPA 738-R-06-020. July 2006.

OCSPP Guideline: 870.2500
Data Requirement: Primary Dermal Irritation

Summary:

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use as an antimicrobial preservative for incorporation into paints or plastics which can then be applied or incorporated into other household and industrial products such as ceramics, wood, plastic, cement plaster and other building materials to protect against mold and mildew. Corning Inc. requests that the requirement for a Primary Dermal Irritation study (OCSPP 870.2500) for copper (II) oxide be satisfied by existing data and information based on the facts that: 1) copper is an endogenous biochemical; 2) the dermal irritation properties of copper(II) have been established with animal testing; 3) there is a history of safe medical, commercial and industrial use of copper; and 4) the potential for skin exposure to copper is low for this use.

Response to Data Requirement:

As an endogenous compound, copper is an integral part of many proteins and enzymes important to cellular respiration, cellular energy metabolism, connective tissue biosynthesis, and iron metabolism (WHO 1998). The EPA RED (2006) indicates that cupric oxide can be classified Toxicity Category III for dermal irritation (PI Index = 1.49). In the European Chemicals Agency (ECHA) dossier for cupric oxide, an OECD guideline 404 study is described in which the test material was not classified as an irritant or corrosive to skin (ECHA 2015). In addition, cupric oxide has been impregnated or plated into textiles like bed linens and socks (Gabbay et al. 2006). No adverse or any other reactions were noted in 100 patients who slept on copper-impregnated sheets. Similarly, no adverse effects were reported in individuals wearing copper-impregnated socks to combat athlete's foot. Copper is used in wound dressings and ointments, as a topical astringent/antiseptic, and in commercial skin care products (Borkow and Okon-Levy 2010; Fiume et al. 2014; Dresher 2006).

Significant dermal exposure to copper is not anticipated in the present use. When copper oxide mixed with aluminoborosilicate glass is heated to very high temperatures, the copper ionizes, becomes a part of the glass matrix and cannot readily be separated from the glass matrix. Therefore, there is very low potential for skin exposure to copper for this use.

Conclusion:

Corning Inc. requests that the requirement for a Primary Dermal Irritation Study for copper(II) oxide be satisfied based on the fact that copper is an endogenous biochemical with a low demonstrated dermal irritation potential. A primary dermal irritation study is not necessary to demonstrate the safety of dermal exposure to copper (II) oxide.

References:

Borkow and Okon-Levy 2010. Copper Oxide Impregnated Wound Dressing: Biocidal and Safety Studies. Wounds 22(12):301-310.

Drescher WH. 2006. Copper and Your Skin: Facelift In A Bottle. Copper Applications in Health and Environment Area. Copper Development Association Newsletter.

European Chemical Agency (ECHA). 2015. Dossier for Copper(II) Oxide. Accessed July 11, 2015. Available: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9eb99a84-d8fb-732d-e044-00144f67d031/AGGR-ee65a25c-efb8-46ee-b81a-a27ae315a487_DISS-9eb99a84-d8fb-732d-e044-00144f67d031.html#AGGR-ee65a25c-efb8-46ee-b81a-a27ae315a487

Fiume et al. 2014. Safety assessment of citric acid, inorganic citrate salts, and alkyl citrate esters as used in cosmetics. IJT 33(Suppl.2):16-46, 2014

Gabbay J, Borkow G, Mishal J, Magen E, Zatcoff R, and Shemer-Avni Y. 2006. Copper Oxide Impregnated Textiles with Potent Biocidal Activities. Journal of Industrial Textiles 35(4): 323-335.

U.S. EPA. 2006. Reregistration Eligibility Decision (RED) for Coppers.

World Health Organization (WHO).1998. Environmental Health Criteria 200. Copper. Section 6.1: Essentiality. IPCS, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland..

OCSPP Guideline: 870.2600
Data Requirement: Dermal Sensitization

Summary:

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use as an antimicrobial preservative for incorporation into paints or plastics which can then be applied or incorporated into other household and industrial products such as ceramics, wood, plastic, cement plaster and other building materials to protect against mold and mildew. Corning Inc. requests that the requirement for a Dermal Sensitization study (OCSPP 870.2600) for copper (II) oxide be satisfied by existing data and information based on the facts that: 1) copper is an endogenous biochemical; 2) the dermal sensitization of copper has been tested in animals; and 3) there is a history of safe commercial and industrial use of copper in textiles, wound-care, skincare, and other products that touch the skin.

Response to Data Requirement:

As an endogenous compound, copper is an integral part of many proteins and enzymes important to cellular respiration, cellular energy metabolism, connective tissue biosynthesis, and iron metabolism (WHO 1998). The EPA RED (2006) indicates that, with the exception of copper naphthalene, copper compounds do not induce skin sensitization. In the European Chemicals Agency (ECHA) dossier for cupric oxide, an OECD guideline 406 study is described in which the test material did not produce a sensitization reaction in the skin of guinea pigs (ECHA 2015). In addition, cupric oxide has been impregnated or plated into textiles like bed linens and socks (Gabbay et al. 2006). No sensitization reactions were noted in 100 patients who slept on copper-impregnated sheets. Similarly, no sensitization was reported in individuals wearing copper-impregnated socks to combat athlete's foot. Copper is also used in wound dressings and ointments, as a topical astringent/antiseptic, and in commercial skin care products with no reports of sensitization reactions (Borkow and Okon-Levy 2010; Fiume et al. 2014; Dresher 2006).

Conclusion:

Corning Inc. requests that the requirement for a Dermal Sensitization Study for copper (II) oxide be satisfied based on the fact that copper is an endogenous biochemical and previous testing characterizes it as non-sensitizing. Copper is used safely in many products that contact the skin. A dermal sensitization study is therefore not necessary to demonstrate the safety of dermal exposure to copper (II) oxide.

References:

Borkow and Okon-Levy 2010. Copper Oxide Impregnated Wound Dressing: Biocidal and Safety Studies. Wounds 22(12):301-310.

Drescher WH. 2006. Copper and Your Skin: Facelift In A Bottle. Copper Applications in Health and Environment Area. Copper Development Association Newsletter.

European Chemical Agency (ECHA). 2015. Dossier for Copper(II) Oxide. Accessed July 11, 2015. Available: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9eb99a84-d8fb-732d-e044-00144f67d031/AGGR-ee65a25c-efb8-46ee-b81a-a27ae315a487_DISS-9eb99a84-d8fb-732d-e044-00144f67d031.html#AGGR-ee65a25c-efb8-46ee-b81a-a27ae315a487

Fiume et al. 2014. Safety assessment of citric acid, inorganic citrate salts, and alkyl citrate esters as used in cosmetics. IJT 33(Suppl.2):16-46, 2014

Gabbay J, Borkow G, Mishal J, Magen E, Zatcoff R, and Shemer-Avni Y. 2006. Copper Oxide Impregnated Textiles with Potent Biocidal Activities. Journal of Industrial Textiles 35(4): 323-335.

U.S. EPA. 2006. Reregistration Eligibility Decision (RED) for Coppers.

World Health Organization (WHO).1998. Environmental Health Criteria 200. Copper. Section 6.1: Essentiality. IPCS, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland..

OCSPP Guideline: 870.6200
Data Requirement: Acute Neurotoxicity

Summary:

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use as an antimicrobial preservative for incorporation into paints or plastics that can then be applied or incorporated into other household and industrial products such as ceramics, wood, plastic, cement plaster and other building materials to protect against mold and mildew. Corning Inc. requests that the requirement for an Acute Neurotoxicity Study (OCSPP 870.6200) for copper (II) oxide be satisfied by existing data and information based on the facts that: 1) copper is an endogenous chemical that is essential in the human diet; 2) copper (II) compounds are not significantly toxic; 3) the bioavailability of copper from the present end use is very low; exposure to excess copper from its use as a material preservative in paints and plastic will not be significant; and 4) studies are available that characterize neurotoxicity of copper in rats and workers.

Response to Data Requirement:

As an endogenous compound, copper is an integral part of many proteins and enzymes important to cellular respiration, cellular energy metabolism, connective tissue biosynthesis, and iron metabolism (WHO 1998). ATSDR (2004) considered an oral daily uptake of 1–3 mg/day necessary to avoid copper deficiency. The Institute of Medicine at the National Academies of Sciences recommends a dietary allowance of 0.9-1.3 mg/day for adults (IOM 2015). These Recommended Dietary Allowances (RDA) are the average daily dietary intake level sufficient to meet the nutrient requirements of 97-98% of healthy individuals. The suggested upper limit for adults is 10 mg copper/day.

Copper (II) compounds are not significantly toxic as demonstrated by the fact that a variety of copper-containing compounds are exempt from the requirement of a tolerance, including metallic copper in the form of chelates of copper citrate and copper gluconate (40 CFR 180.1021 (a) (b) (c) (d); EPA, 2006).

The use of copper (II) oxide as a TGAI in treated paint and plastic articles is not expected to increase exposure above the normal dietary exposure. This is due in part to the processing of cupric oxide and aluminoborosilicate glass in the end use product, which involves heating to very high temperatures so that copper ionizes and then becomes a part of the glass matrix and cannot readily be separated from the glass.

ATSDR (2004) has summarized two neurotoxicity studies of copper in rodents, as well as information about the effects of high copper exposure in people. In 30-day study of rats fed a diet containing 23 mg Cu/kg bw/day as copper sulfate, no effects on neurobehavioral performance were observed, including spontaneous motor activity, learning ability, or relearning capacity and memory. Levels of dopamine and norepinephrine in the brain were also not affected by dietary copper. In another study where Sprague-Dawley female rats were exposed to 36 mg Cu/kg/day as copper sulfate

for 11 months in drinking water, the level of the dopamine metabolite 3,4-dihydroxyphenylacetic acid in the corpus striatum was 25% lower compared to control rats. This effect suggests a perturbation of the dopaminergic pathway, however the level of corpus striatial dopamine itself was unaffected by copper sulfate exposure (ATSDR 2004). Evidence of neurological impairment in the form of headache, vertigo, and drowsiness has been observed in factory workers exposed to 111–434 mg/m^3 copper dust (ATSDR 2004).

Conclusion:

Corning Inc. requests that the requirement for an Acute Neurotoxicity study for copper (II) oxide be satisfied based on the fact that copper is an essential nutrient with known toxicological properties. The daily copper requirement of 0.9-1.3 mg is greater than the expected exposure to copper from use of the active ingredient as a materials preservative. An additional neurotoxicity study is not necessary to characterize this endpoint for copper(II) oxide.

References:

Agency for Toxic Substances and Disease Registry (ATSDR). 2004. Toxicological profile for copper (update). Chapter 3: Health effects. US Department of Health and Human Services. Public Health Service.

Institute of Medicine (IOM). 2015. Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Vitamins Food and Nutrition Board, Institute of Medicine, National Academies. Accessed July 2015.

World Health Organization (WHO).1998. Environmental Health Criteria 200. Copper. Section 6.1: Essentiality. IPCS, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland..

OCSPP Guideline: 870.3100
Data Requirement: 90-Day Oral Toxicity

Summary:

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use as an antimicrobial preservative for incorporation into paints or plastics which can then be applied or incorporated into other household and industrial products such as ceramics, wood, cement plaster and other building materials to protect against mold and mildew. Corning Inc. requests that the requirement for a 90-day Oral Toxicity study (OCSPP 870.3100) for copper (II) oxide be satisfied by existing data and information based on the facts that: 1) copper is an endogenous compound that is a dietary requirement for animals; 2) copper compounds are exempt from the requirement of a tolerance; 3) the potential for exposure to copper is low for the proposed use.

Response to Data Requirement:

As an endogenous compound, copper is an integral part of many proteins and enzymes important to cellular respiration, cellular energy metabolism, connective tissue biosynthesis and iron metabolism (WHO 1998). ATSDR (2004) considers an oral daily uptake of 1–3 mg/day necessary to avoid copper deficiency. The Institute of Medicine at the National Academies of Sciences recommends a dietary allowance of 0.9 mg/day for adult women, 1.0 mg/day for pregnant women, and 1.3 mg/day for lactating women (IOM 2015). These Recommended Dietary Allowances (RDA) are the average daily dietary intake level sufficient to meet the nutrient requirements of 97-98% of healthy individuals. The suggested upper limit for adults is 10 mg copper/day.

Copper compounds are of low oral toxicity as demonstrated by the fact that a variety of copper-containing compounds are exempt from the requirement of a tolerance, including metallic copper in the form of chelates of copper citrate and copper gluconate (40 CFR 180.1021 (a) (b) (c) (d); EPA, 2006). Cupric oxide was formerly exempt from the requirement of a tolerance under 40 CFR §180.1021(4)(b); when EPA published the 2006 RED for copper it was removed from the list of exempt compounds because there were no cupric oxide products registered for food use at that time. The evaluation of copper in the Human Health Chapter of the EPA Reregistration Eligibility Decision (RED) document indicates that no toxicological endpoints were established for copper residues (EPA 2006). Thus there is no toxicological concern from potential oral exposure to copper.

The use of copper (II) oxide as a TGAI in treated paint and plastic articles is not expected to increase estimated dietary exposure above the normal background dietary levels. This is due in part to the processing of cupric oxide in the end use product. When cupric oxide mixed with aluminoborosilicate glass is heated to very high temperatures, copper ions form and become a part of the glass matrix; the copper and glass cannot readily be separated. Therefore, the potential for exposure to copper is very low.

Conclusion:

Corning Inc. requests that the requirement for a 90-day Oral Toxicity study for copper (II) oxide be satisfied based on the fact that copper is a dietary requirement, an endogenous chemical, and copper compounds have a low toxicity profile and long history of safe use in pesticides. Furthermore, the potential for oral exposure to copper is low for the present end use. Therefore, a 90-day oral toxicity study is not necessary for copper (II) oxide.

References:

Agency for Toxic Substances and Disease Registry (ATSDR). 2004. Toxicological profile for copper (update). Chapter 3: Health effects. US Department of Health and Human Services. Public Health Service.

Copper Development Association (CDA). 2015. Uses of Copper Compounds: Other Copper Compounds

U.S. EPA. 2006. Reregistration Eligibility Decision (RED) for Coppers.

World Health Organization (WHO).1998. Environmental Health Criteria 200. Copper. Section 6.1: Essentiality. IPCS, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland..

OCSPP Guideline: 870.3250
Data Requirement: 90-Day Dermal Toxicity

Summary:

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use as an antimicrobial preservative for incorporation into paints or plastics which can then be applied or incorporated into other household and industrial products such as ceramics, wood, cement plaster and other building materials to protect against mold and mildew. Corning Inc. requests that the requirement for a 90-day Dermal Toxicity study (OCSPP 870.3250) be satisfied by existing data and information based on the facts that: 1) copper is an endogenous compound; 2) copper compounds are currently registered by EPA for multiple pesticidal uses and have a low toxicity profile; 3) copper is a ubiquitous substance and used in many medical and consumer products; 4) copper is poorly absorbed through the skin; and 5) the potential for exposure to copper is low for the proposed use.

Response to Data Requirement:

As an endogenous compound, copper is an integral part of many proteins and enzymes important to cellular respiration, cellular energy metabolism, connective tissue biosynthesis, and iron metabolism (WHO 1998). Copper compounds are of low toxicity as demonstrated by the fact that a variety of copper-containing compounds are exempt from the requirement of a tolerance under 40 CFR §180.1021(4)(b). Copper compounds are registered for antimicrobial pesticidal use in wood paint, glue, building materials, construction materials, and water treatment wherein the active copper ion functions as a mildewcide, bactericide, or anti-fouling agent (EPA 2006). The evaluation of copper in the Human Health Chapter of the EPA Reregistration Eligibility Decision (RED) document indicates that no toxicological endpoints were established for copper residues (EPA 2006). Thus there is no toxicological concern from potential dermal exposure to copper.

In addition to pesticides, copper is used in wound dressings and ointments, as a topical astringent/antiseptic, and in commercial skin care products (Borkow and Okon-Levy 2010; Fiume et al. 2014; Dresher 2006). Copper has long been used in ceramics for imparting colors into glasses, glazes and enamels (CDA 2015). It is also incorporated into mineral supplements for animal diets.

Systemic exposure to copper oxide or copper ions is not anticipated. In vitro studies and in vivo dermal application of copper salts or dermal exposure to metallic copper fumes suggest that copper is poorly absorbed through the skin (SCOEL 2014; ATSDR 2004). In one study, less than 6% of copper deposited on *ex vivo* human skin samples was absorbed (SCOEL 2014). Thus, systemic copper exposure is unlikely. In addition, there is little potential for exposure to copper from the end use product. Cupric oxide is mixed with aluminoborosilicate glass and heated to very high temperatures at which point the copper ionizes and cannot readily be separated from the glass. Therefore, the potential for dermal exposure to copper, particularly for prolonged or repeated contact, is very low.

Conclusion:

Corning Inc. requests that the requirement for a 90-day Dermal Toxicity study for copper (II) oxide be satisfied based on the low toxicity profile and long history of safe use of copper in a variety of products. Dermal contact with copper is common with other products and the potential for systemic copper exposure is low in general and specifically low for the present end use. A 90-day dermal exposure study is not necessary to demonstrate the safety of repeated dermal exposure to copper (II) oxide.

References:

40 CFR 180.1021 Copper; exemption from the requirement of a tolerance.

Agency for Toxic Substances and Disease Registry (ATSDR). 2004. Toxicological profile for copper (update). Chapter 3: Health effects. US Department of Health and Human Services. Public Health Service.

Copper Development Association (CDA). 2015. Uses of Copper Compounds: Other Copper Compounds

Borkow and Okon-Levy 2010. Copper Oxide Impregnated Wound Dressing: Biocidal and Safety Studies. Wounds 22(12):301-310.

Drescher WH. 2006. Copper and Your Skin: Facelift In A Bottle. Copper Applications in Health and Environment Area. Copper Development Association Newsletter.

Fiume et al. 2014. Safety assessment of citric acid, inorganic citrate salts, and alkyl citrate esters as used in cosmetics. IJT 33(Suppl.2):16-46, 2014

Scientific Committee on Occupational Exposure Limits (SCOEL). 2014. Recommendation from the Scientific Committee on Occupational Exposure Limits for Copper and its inorganic compounds. European Commission. SCOEL/SUM/171. March 2014

U.S. EPA. 2006. Reregistration Eligibility Decision (RED) for Coppers.

World Health Organization (WHO).1998. Environmental Health Criteria 200. Copper. Section 6.1: Essentiality. IPCS, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland.

OCSPP Guideline: 870.3465
Data Requirement: 90-Day Inhalation Toxicity

Summary:

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use as an antimicrobial preservative for incorporation into paints or plastics which can then be applied or incorporated into other household and industrial products such as ceramics, wood, plastic, cement plaster and other building materials to protect against mold and mildew. Corning Inc. requests that the requirement for a 90-Day Inhalation Toxicity study (OCSPP 870.3465) for copper (II) oxide be satisfied by existing data and information based on the facts that: 1) copper is a ubiquitous naturally occurring metal that is exempt from the requirement of a tolerance for most uses; and 2) there is no evidence for systemic toxicity of copper (II) oxide by the inhalation route of exposure and 3) the potential for systemic exposure to copper is low for the proposed use.

Response to Data Requirement:

Copper is of low toxicity as demonstrated by the fact that a variety of copper-containing compounds are exempt from the requirement of a tolerance, including metallic copper in the form of chelates of copper citrate and copper gluconate (40 CFR 180.1021 (a) (b) (c) (d); EPA, 2006). The evaluation of copper in the Human Health Chapter of the EPA Reregistration Eligibility Decision (RED) document indicates that no toxicological endpoints were established for copper residues (EPA 2006). Thus there is no toxicological concern from potential exposure by inhalation to copper.

Inhalation of copper as dusts or mists is likely to be irritating to the respiratory system (EPA 2006), but there is no evidence that it causes systemic toxicity.

Systemic exposure to copper oxide is not anticipated. Cupric oxide is mixed with aluminoborosilicate glass and heated to very high temperatures at which point the copper ionizes and cannot readily be separated from the glass. Therefore, the potential for inhalation exposure to copper, particularly for prolonged or repeated contact, is very low.

Conclusion:

Corning Inc. requests that the requirement for a 90-Day Inhalation Toxicity Study for copper (II) oxide be satisfied based on the fact that there is a long history of using copper in pesticides with no toxicological endpoints established and because the systemic exposure will be low for this route. Therefore, an additional 90-day inhalation toxicity study is not necessary for copper(II) oxide.

References:

U.S. EPA. 2006. Reregistration Eligibility Decision (RED) for Coppers. EPA 738-R-06-020. July 2006.

OCSPP Guideline: 870.3700
Data Requirement: Prenatal Developmental Toxicity Study

Summary:

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use as an antimicrobial preservative for incorporation into paints or plastics which can then be applied or incorporated into other household and industrial products such as ceramics, wood, plastic, cement plaster and other building materials to protect against mold and mildew. Corning Inc. requests that the requirement for a Prenatal Developmental Toxicity study (OCSPP 870.3700) for copper (II) oxide be satisfied by existing data and information based on the facts that: 1) copper is an endogenous chemical that is essential in the human diet; 2) the bioavailability of copper from the present end use is very low; therefore women of child-bearing age will not be exposed to excess copper from its use as a material preservative; and 3) copper is low in toxicity.

Response to Data Requirement:

As an endogenous compound, copper is an integral part of many proteins and enzymes important to cellular respiration, cellular energy metabolism, connective tissue biosynthesis and iron metabolism (WHO 1998). ATSDR (2004) considers an oral daily uptake of 1–3 mg/day necessary to avoid copper deficiency. The Institute of Medicine at the National Academies of Sciences recommends a dietary allowance of 0.9 mg/day for adult women, 1.0 mg/day for pregnant women, and 1.3 mg/day for lactating women (IOM 2015). These Recommended Dietary Allowances (RDA) are the average daily dietary intake level sufficient to meet the nutrient requirements of 97-98% of healthy individuals. The suggested upper limit for adults is 10 mg copper/day.

The use of copper (II) oxide as a TGAI in treated paint and plastic articles is not expected to increase dietary copper intake in women of child-bearing age above these required dietary levels. This is due in part to the processing of cupric oxide and aluminoborosilicate glass in the end use product, which involves heating to very high temperatures so that the copper ionizes and is subsequently bound within the glass matrix and not easily separated. Therefore, the potential for exposure to copper is very low.

Furthermore, copper is of low oral toxicity as demonstrated by the fact that a variety of copper-containing compounds are exempt from the requirement of a tolerance, including metallic copper in the form of chelates of copper citrate and copper gluconate (40 CFR 180.1021 (a) (b) (c) (d); EPA, 2006). The evaluation of copper in the Human Health Chapter of the EPA Reregistration Eligibility Decision (RED) document indicated that no toxicological endpoints were established for copper residues (EPA 2006). The RED states that “available reproductive and developmental studies by the oral route of exposure generally indicate that the main concern in animals for reproductive and

teratogenic effects of copper has usually been associated with the deficiency rather than the excess of copper."

Conclusion:

Corning Inc. requests that the requirement for a Prenatal Developmental Toxicity study for copper (II) oxide be satisfied based on the fact that copper is an essential component of the diet, the potential exposure to copper is low for women of child-bearing age, and many copper compounds are exempt from the requirement of a tolerance. The daily copper requirement for women is far greater than the expected exposure from use of the active ingredient as a materials preservative. An additional prenatal developmental toxicity study is not necessary for copper (II) oxide.

References :

40 CFR 180.1021 Copper; exemption from the requirement of a tolerance.

Agency for Toxic Substances and Disease Registry (ATSDR). 2004. Toxicological profile for copper (update). Chapter 3: Health effects. US Department of Health and Human Services. Public Health Service.

Institute of Medicine (IOM). 2015. Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Vitamins Food and Nutrition Board, Institute of Medicine, National Academies. Accessed July 2015.

U.S. EPA. 2006. Reregistration Eligibility Decision (RED) for Coppers.
EPA 738-R-06-020. July 2006.

World Health Organization (WHO).1998. Environmental Health Criteria 200. Copper.
IPCS, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland.

OCSPP Guideline: 870.3800
Data Requirement: Reproduction and Fertility Effects

Summary:

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use as an antimicrobial preservative for incorporation into paints or plastics which can then be applied or incorporated into other household and industrial products such as ceramics, wood, cement plaster and other building materials to protect against mold and mildew. Corning Inc. requests that the requirement for a toxicity study of copper (II) oxide on Reproduction and Fertility Effects (OCSPP 870.3800) be satisfied by existing data and information based on the facts that: 1) copper is an endogenous chemical that is essential in the human diet; 2) the bioavailability of copper from the present end use is very low; therefore women of child-bearing age will not be exposed to excess copper; and 3) copper is low in toxicity.

Response to Data Requirement:

As an endogenous compound, copper is an integral part of many proteins and enzymes important to cellular respiration, cellular energy metabolism, connective tissue biosynthesis and iron metabolism (WHO 1998). ATSDR (2004) considers an oral daily uptake of 1–3 mg/day necessary to avoid copper deficiency. The Institute of Medicine at the National Academies of Sciences recommends a dietary allowance of 0.9 mg/day for adult men and women, 1.0 mg/day for pregnant women, and 1.3 mg/day for lactating women (IOM 2015). These Recommended Dietary Allowances (RDA) are the average daily dietary intake level sufficient to meet the nutrient requirements of 97-98% of healthy individuals. The suggested upper limit for adults is 10 mg copper/day.

The use of copper (II) oxide as a TGAI in treated paint and plastic articles is not expected to increase dietary exposure for women of child bearing age. This is due in part to the processing of copper and aluminoborosilicate glass in the end use product, which involves heating to very high temperatures so that the copper ionizes and cannot be readily separated from the glass matrix. The copper is bound in the glass matrix and therefore, the potential for exposure to copper is very low.

Furthermore, copper is of low oral toxicity as demonstrated by the fact that a variety of copper-containing compounds are exempt from the requirement of a tolerance, including metallic copper in the form of chelates of copper citrate and copper gluconate (40 CFR 180.1021 (a) (b) (c) (d); EPA, 2006). The evaluation of copper in the Human Health Chapter of the EPA Reregistration Eligibility Decision (RED) document indicated that no toxicological endpoints were established for copper residues (EPA 2006). The RED states that “available reproductive and developmental studies by the oral route of exposure generally indicate that the main concern in animals for reproductive and teratogenic effects of copper has usually been associated with the deficiency rather than the excess of copper.”

Conclusion:

Corning Inc. requests that the requirement for a Reproduction and Fertility Effects study for copper (II) oxide be satisfied based on the fact that copper is an essential nutritional requirement and any additional exposure from this present use will be insignificant. Copper compounds are exempt from the requirement of a tolerance. An additional reproductive toxicity study is not necessary for copper (II) oxide.

References:

40 CFR 180.1021 Copper; exemption from the requirement of a tolerance.

Agency for Toxic Substances and Disease Registry (ATSDR). 2004. Toxicological profile for copper (update). Chapter 3: Health effects. US Department of Health and Human Services. Public Health Service.

Institute of Medicine (IOM). 2015. Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Vitamins Food and Nutrition Board, Institute of Medicine, National Academies. Accessed July 2015.

U.S. EPA. 2006. Reregistration Eligibility Decision (RED) for Coppers.
EPA 738-R-06-020. July 2006.

World Health Organization (WHO).1998. Environmental Health Criteria 200. Copper. Section 6.1: Essentiality. IPCS, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland..

OCSPP Guideline: 870.4200
Data Requirement: Carcinogenicity

Summary:

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use as an antimicrobial preservative for incorporation into paints or plastics which can then be applied or incorporated into other household and industrial products such as ceramics, wood, cement plaster and other building materials to protect against mold and mildew. Corning Inc. requests that the requirement for a Carcinogenicity study of copper (II) oxide (OCSPP 870.4200) be satisfied by existing data and information based on the facts that: 1) copper is an endogenous chemical that is essential in the human diet; 2) the low toxicity of copper has been previously established; and 3) the bioavailability of copper from the present end use is very low.

Response to Data Requirement:

As an endogenous compound, copper is an integral part of many proteins and enzymes important to cellular respiration, cellular energy metabolism, connective tissue biosynthesis and iron metabolism (WHO 1998). ATSDR (2004) considers an oral daily uptake of 1–3 mg/day necessary to avoid copper deficiency. The Institute of Medicine at the National Academies of Sciences recommends a dietary allowance of 0.9 mg/day for adult men and women, 1.0 mg/day for pregnant women, and 1.3 mg/day for lactating women (IOM 2015). These Recommended Dietary Allowances (RDA) are the average daily dietary intake level sufficient to meet the nutrient requirements of 97-98% of healthy individuals. The suggested upper limit for adults is 10 mg copper/day.

Furthermore, copper is of low oral toxicity as demonstrated by the fact that a variety of copper-containing compounds are exempt from the requirement of a tolerance, including metallic copper in the form of chelates of copper citrate and copper gluconate (40 CFR 180.1021 (a) (b) (c) (d); EPA, 2006). The evaluation of copper in the Human Health Chapter of the EPA Reregistration Eligibility Decision (RED) document indicated that no toxicological endpoints were established for copper residues (EPA 2006). The RED states that “there is no evidence of copper or its salts being carcinogenic or posing any other systemic toxicity in animals having normal copper homeostasis.”

The use of copper (II) oxide as a TGAI in treated paint and plastic articles is not expected to increase people’s dietary exposure. This is due in part to the processing of copper (II) oxide and aluminoborosilicate glass in the end use product, which involves heating to very high temperatures so that the copper ionizes and cannot be readily separated from the glass. The copper is bound in the glass matrix and therefore, the use of the EP or treated article is not likely to result in repeated human exposure over a considerable portion of the human lifespan.

Conclusion:

Corning Inc. requests that the requirement for a Carcinogenicity study for copper (II) oxide be satisfied based on the fact that copper is an essential nutritional requirement that is exempt from the requirement of a tolerance, and any additional exposure from this present use is likely to be insignificant. An additional cancer study is not necessary for copper (II) oxide.

References:

40 CFR 180.1021 Copper; exemption from the requirement of a tolerance.

Agency for Toxic Substances and Disease Registry (ATSDR). 2004. Toxicological profile for copper (update). Chapter 3: Health effects. US Department of Health and Human Services. Public Health Service.

Institute of Medicine (IOM). 2015. Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Vitamins Food and Nutrition Board, Institute of Medicine, National Academies. Accessed July 2015.

U.S. EPA. 2006. Reregistration Eligibility Decision (RED) for Coppers.
EPA 738-R-06-020. July 2006.

World Health Organization (WHO).1998. Environmental Health Criteria 200. Copper. Section 6.1: Essentiality. IPCS, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland..

OCSPP Guideline: 870.5100
Data Requirement: Bacterial Reverse Mutation Test

Summary:

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use as an antimicrobial preservative for incorporation into paints or plastics which can then be applied or incorporated into other household and industrial products such as ceramics, wood, cement plaster and other building materials to protect against mold and mildew. Corning Inc. requests that the requirement for a Bacterial Reverse Mutation study (OCSPP 870.5100) be satisfied by existing data and information based on the facts that: 1) copper is an endogenous chemical that is an essential nutrient in the human diet; 2) the bioavailability of copper from the present end use is very low; and 3) copper compounds were not mutagenic in most studies in bacteria.

Response to Data Requirement:

As an endogenous compound, copper is an integral part of many proteins and enzymes important to cellular respiration, cellular energy metabolism, connective tissue biosynthesis, and iron metabolism (WHO 1998). ATSDR (2004) considered an oral daily uptake of 1–3 mg/day necessary to avoid copper deficiency. The Institute of Medicine at the National Academies of Sciences recommends a dietary allowance of 0.9-1.3 mg/day for adults (IOM 2015). These Recommended Dietary Allowances (RDA) are the average daily dietary intake level sufficient to meet the nutrient requirements of 97-98% of healthy individuals. The suggested upper limit for adults is 10 mg copper/day. The use of copper (II) oxide as a TGAI in treated paint and plastic articles is not expected to increase exposure to copper levels presently encountered in the diet. This is due in part to the processing of cupric oxide and aluminoborosilicate glass in the end use product, which involves heating to very high temperatures so that the copper ionizes and cannot be readily separated from the glass matrix. Therefore, the potential for exposure to copper is very low.

Copper compounds are not generally mutagenic in bacterial reverse mutation assays. Copper sulfate and copper chloride produced negative results in *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 with or without metabolic activation, even at cytotoxic concentrations or at the limit of solubility (SCOEL 2014). EPA's IRIS database reported on a study in which there was no increase in reverse mutations in *Escherichia coli* or *S. typhimurium* strains TA98, TA1535, TA1537 and TA1538 when they were incubated with up to 5 mg copper quinolinolate/plate and in *S. typhimurium* TA98 and TA100 incubated with up to 5 mg copper sulfate/plate (US EPA 1988).

Conclusion:

Corning Inc. requests that the requirement for an *In vitro* Bacterial Reverse Mutation Assay for copper (II) oxide be satisfied based on the fact that copper is a normal component of the diet and an essential nutritional requirement. The daily copper requirement of 0.9-1.3 mg is greater than the expected exposure from use of the active ingredient as a materials preservative. Existing reverse mutation studies of other copper compounds are negative. An additional bacterial reverse mutation study is not necessary for copper (II) oxide.

References:

Agency for Toxic Substances and Disease Registry (ATSDR). 2004. Toxicological profile for copper (update). Chapter 3: Health effects. US Department of Health and Human Services. Public Health Service.

Institute of Medicine (IOM). 2015. Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Vitamins Food and Nutrition Board, Institute of Medicine, National Academies. Accessed July 2015.

Scientific Committee on Occupational Exposure Limits (SCOEL). 2014. Recommendation from the Scientific Committee on Occupational Exposure Limits for Copper and its inorganic compounds. European Commission. SCOEL/SUM/171. March 2014

U.S. EPA. 1988. Integrated Risk Information System (IRIS) document 0368. Copper; CASRN 7440-50-8. Available: http://www.epa.gov/iris/subst/0368.htm

World Health Organization (WHO).1998. Environmental Health Criteria 200. Copper. Section 6.1: Essentiality. IPCS, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland..

OCSPP Guideline: 870.5300
Data Requirement: *In vitro* Mammalian Cell Gene Mutation Test

Summary:

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use as an antimicrobial preservative for incorporation into paints or plastics that can then be applied or incorporated into other household and industrial products such as ceramics, wood, cement plaster and other building materials to protect against mold and mildew. Corning Inc. requests that the requirement for an *In vitro* Mammalian Cell Gene Mutation Test (OCSPP 870.5300) be satisfied by existing data and information based on the facts that: 1) copper is an endogenous chemical that is essential in the human diet; 2) the bioavailability of copper (II) oxide from the present end use is very low and so exposure will not be significant; and 3) mammalian cell mutation tests have been carried out for other copper compounds.

Response to Data Requirement:

As an endogenous compound, copper is an integral part of many proteins and enzymes important to cellular respiration, cellular energy metabolism, connective tissue biosynthesis, and iron metabolism (WHO 1998). ATSDR (2004) considered an oral daily uptake of 1–3 mg/day necessary to avoid copper deficiency. The Institute of Medicine at the National Academies of Sciences recommends a dietary allowance of 0.9-1.3 mg/day for adults (IOM 2015). These Recommended Dietary Allowances (RDA) are the average daily dietary intake level sufficient to meet the nutrient requirements of 97-98% of healthy individuals. The suggested upper limit for adults is 10 mg copper/day. The use of copper (II) oxide as a TGAI in treated paint and plastic articles is not expected to increase estimated dietary exposure above the normal dietary exposure. This is due in part to the processing of cupric oxide and aluminoborosilicate glass in the end use product, which involves heating to very high temperatures so that the copper ionizes and cannot be readily separated from the glass matrix. Therefore, the potential for exposure to copper is very low.

Positive results have been found in mammalian cell studies of copper's genotoxicity (ATSDR 2004). Copper chloride affected DNA synthesis in Chinese hamster ovary cells in the absence of metabolic activation. Copper sulfate and copper nitrate increased the occurrence of DNA strand breaks in rat hepatocytes and Chinese hamster V79 cells, respectively, in the absence of metabolic activation.

Conclusion:

Corning Inc. requests that the requirement for an *In vitro* Mammalian Cell Gene Mutation Test for copper (II) oxide be satisfied based on the fact that copper is a normal component of the diet and an essential nutritional requirement. The daily copper requirement of 0.9-1.3 mg is greater than the expected exposure to copper from use of the active ingredient as a materials preservative. In vitro mammalian cell mutation assays indicate that copper compounds have DNA damaging properties. A new mutation assay on copper (II) oxide is not necessary to determine this.

References:

Agency for Toxic Substances and Disease Registry (ATSDR). 2004. Toxicological profile for copper (update). Chapter 3: Health effects. US Department of Health and Human Services. Public Health Service.

Institute of Medicine (IOM). 2015. Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Vitamins Food and Nutrition Board, Institute of Medicine, National Academies. Accessed July 2015.

U.S. EPA. 1988. Integrated Risk Information System (IRIS) document 0368. Copper; CASRN 7440-50-8. Available: http://www.epa.gov/iris/subst/0368.htm

World Health Organization (WHO).1998. Environmental Health Criteria 200. Copper. Section 6.1: Essentiality. IPCS, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland..

OCSPP Guideline: 870.5375
Data Requirement: *In vitro* Mammalian Chromosome Aberration Test

Summary:

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use as an antimicrobial preservative for incorporation into paints or plastics that can then be applied or incorporated into other household and industrial products such as ceramics, wood, cement plaster and other building materials to protect against mold and mildew. Corning Inc. requests that the requirement for an *In vitro Mammalian Chromosome Aberration Test* (OCSPP 870.5375) be satisfied by existing data and information based on the facts that: 1) copper is an endogenous chemical that is essential in the human diet; 2) the bioavailability of copper from the present end use is very low; exposure to excess copper from its use as a material preservative in paints and plastic will not be significant; and 3) chromosomal aberration studies have been carried out previously for copper compounds.

Response to Data Requirement:

As an endogenous compound, copper is an integral part of many proteins and enzymes important to cellular respiration, cellular energy metabolism, connective tissue biosynthesis, and iron metabolism (WHO 1998). ATSDR (2004) considered an oral daily uptake of 1–3 mg/day necessary to avoid copper deficiency. The Institute of Medicine at the National Academies of Sciences recommends a dietary allowance of 0.9-1.3 mg/day for adults (IOM 2015). These Recommended Dietary Allowances (RDA) are the average daily dietary intake level sufficient to meet the nutrient requirements of 97-98% of healthy individuals. The suggested upper limit for adults is 10 mg copper/day. The use of copper (II) oxide as a TGAI in treated paint and plastic articles is not expected to increase estimated dietary exposure above the normal dietary exposure. This is due in part to the processing of cupric oxide and aluminoborosilicate glass in the end use product, which involves heating to very high temperatures so that the copper ionizes and cannot be readily separated from the glass matrix. Therefore, the potential for exposure to copper is very low.

Studies of copper's clastogenicity have been conducted previously. U.S. EPA's IRIS database cites a study in which chromosomal aberrations were induced in isolated rat hepatocytes incubated with copper sulfate (US EPA 1988). A study cited by ATDSR (2004) found significant increases in the frequency of chromosomal aberrations in chick bone marrow cells after intraperitoneal (i.p.) injection or oral exposure to copper sulfate, and in Swiss mouse bone marrow cells after i.p. or subcutaneous exposure. Similarly, an increase in sister chromatid exchange was reported in Chinese hamster cells (ATSDR 2004).

Conclusion:

Corning Inc. requests that the requirement for an in vitro Mammalian Chromosome Aberration Test for copper (II) oxide be satisfied based on the fact that copper is a normal component of the diet and an essential nutritional requirement. The daily copper requirement of 0.9-1.3 mg is greater than the expected exposure to copper from use of the active ingredient as a materials preservative. Finally, data exist already on the clastogenicity of copper compounds in mammalian cells. An additional in vitro mammalian chromosome aberration assay is not necessary to characterize this endpoint for copper (II) oxide.

References:

Agency for Toxic Substances and Disease Registry (ATSDR). 2004. Toxicological profile for copper (update). Chapter 3: Health effects. US Department of Health and Human Services. Public Health Service.

Institute of Medicine (IOM). 2015. Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Vitamins Food and Nutrition Board, Institute of Medicine, National Academies. Accessed July 2015.

U.S. EPA. 1988. Integrated Risk Information System (IRIS) document 0368. Copper; CASRN 7440-50-8. Available: http://www.epa.gov/iris/subst/0368.htm

World Health Organization (WHO).1998. Environmental Health Criteria 200. Copper. Section 6.1: Essentiality. IPCS, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland..

OCSPP Guideline: 870.7800
Data Requirement: Immunotoxicity

Summary:

Copper (II) oxide is a technical grade active ingredient (TGAI) intended for use as an antimicrobial preservative for incorporation into paints or plastics that can then be applied or incorporated into other household and industrial products such as ceramics, wood, plastic, cement plaster and other building materials to protect against mold and mildew. Corning Inc. requests that the requirement for an Immunotoxicity Study (OCSPP 870.7800) be satisfied by existing data and information based on the facts that: 1) copper is an endogenous chemical that is essential in the human diet; 2) the bioavailability of copper from the present end use is very low; and 3) immunotoxicity of copper compounds has been characterized previously.

Response to Data Requirement:

As an endogenous compound, copper is an integral part of many proteins and enzymes important to cellular respiration, cellular energy metabolism, connective tissue biosynthesis, and iron metabolism (WHO 1998). ATSDR (2004) considered an oral daily uptake of 1–3 mg/day necessary to avoid copper deficiency. The Institute of Medicine at the National Academies of Sciences recommends a dietary allowance of 0.9-1.3 mg/day for adults (IOM 2015). These Recommended Dietary Allowances (RDA) are the average daily dietary intake level sufficient to meet the nutrient requirements of 97-98% of healthy individuals. The suggested upper limit for adults is 10 mg copper/day. The use of copper (II) oxide as a TGAI in treated paint and plastic articles is not expected to increase exposure above the normal dietary levels. This is due in part to the processing of cupric oxide and aluminoborosilicate glass in the end use product, which involves heating to very high temperatures so that the copper cannot be readily separated from the glass matrix. Therefore, the potential for exposure to copper is very low.

There is some evidence in mouse studies of an impaired immune response following acute or subacute exposure to high levels of copper sulfate by inhalation and a subsequent bacterial challenge. Similarly, two subacute studies of mice exposed to high doses of copper sulfate via drinking water showed effects on immune functioning (ATSDR 2004). It is notable that the inhibition of immune responses is a typical effect of cations, rather than a specific reaction to copper itself, and has been noted in other trace metals (US EPA 2006).

Conclusion:

Corning Inc. requests that the requirement for an Immunotoxicity study for copper (II) oxide be satisfied based on the fact that copper is a normal component of the diet and an essential nutritional requirement. The daily copper requirement of 0.9-1.3 mg is greater than the expected exposure to copper from use of the active ingredient as a materials preservative. Existing animal studies suggest immune-suppression after inhalation or dietary exposure to high doses of copper. An additional immunotoxicity study is not necessary to characterize this endpoint for copper(II) oxide.

References:

Agency for Toxic Substances and Disease Registry (ATSDR). 2004. Toxicological profile for copper (update). Chapter 3: Health effects. US Department of Health and Human Services. Public Health Service.

Institute of Medicine (IOM). 2015. Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Vitamins Food and Nutrition Board, Institute of Medicine, National Academies of Science. Accessed July 2015.

U.S. EPA. 2006. Reregistration Eligibility Decision (RED) for Coppers.

World Health Organization (WHO).1998. Environmental Health Criteria 200. Copper. Section 6.1: Essentiality. IPCS, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland..